from the reference array and a mixture of diverse cleaved biological polymers from the test array;

(iv) measuring presence of diverse cleaved biological polymers from the test array as an indicator of the efficiency of the first synthesis procedure and measuring presence of diverse cleaved biological polymers from the reference array as an indicator of the efficiency of the second synthesis procedure, thereby determining whether a difference between the first and second synthesis procedure affects the efficiency of the second synthesis procedure.

I. Status of the Application

Claims 1-8, 10-15 and 37-39 are presently pending in the application. Claims 1-8, 10-15 and 37-39 stand rejected under 35 U.S.C. § 112, first paragraph for various reasons of record. Claims 1-8, 10-15 and 37-39 stand rejected under 35 U.S.C. § 102(e) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as being unpatentable over Lam et al. US Patent No. 5,650,489 (102(e) date of at least 6/19/91). Claims 1-8, 10-15 and 37-39 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lam et al. US Patent No. 5,650,489 (102(e) date of at least 6/19/91) in view of Holmes US Patent No. 5,679,773 and Applicants' disclosure of the prior art teachings.

Applicants have amended the claims under consideration to more clearly define and distinctly characterize Applicants' novel invention. Support for the amendments to claims 1 and 10 is found throughout the specification, for example, at pages 14-15. The amendments add no new matter.

Applicants respectfully request entry and consideration of the foregoing amendments to place the case in allowance, or alternatively, to better place the case in condition for appeal.

II. The Rejections of the Claims Under 35 U.S.C. § 112, First Paragraph

At page 2, paragraph 5 of the Office Action claims 1-8, 10-15 and 37-39 stand rejected under 35 U.S.C. § 112, first paragraph. At page 2, paragraph 6, claims 1-8, 10-15 and 37-39 stand rejected under 35 U.S.C. § 112, first paragraph. As to the first rejection, the Examiner states that the claims encompass a genus that is indefinitely large because the specification only discloses peptide and nucleotide libraries. Regarding the second rejection, the Examiner states that the specification enables nucleotides, peptides and peptide nucleic acids but does not reasonably provide enablement of an array of diverse polymers.

Applicants respectfully traverse the Examiner's rejection under § 112 first paragraph. Applicant maintains based on the reasons of record that the phrase "array of diverse polymers" fully meets § 112 first paragraph. Although applicants disagree with the Examiner's rejection, applicants have amended claims 1 and 10 solely to advance prosecution in this application by specifying the compositions of the diverse biological polymers. "The specification provides at page 14 line 28 to page 15, lines 13 that biological polymers are composed of biological monomers that include natural and synthetic amino acids, nucleotides, nucleosides, phosphoramidites, and carbohydrates. Applicants respectfully submit that claims as amended to include the terms nucleotides, nucleosides, phosphoramidites, carbohydrates or natural or synthetic amino acids fully meet the written description and enablement requirements of 35

U.S.C. In view of the above, applicants respectfully request withdrawal of the rejections of claims 1-8, 10-15 and 37-39 under 35 U.S.C. § 112, first paragraph.

III. Claims 1-8, 10-15 and 37-39 Are Patentable over Lam et al.

At page 2, paragraph 8, claims 1-8, 10-15 and 37-39 stand rejected under 35 U.S.C. § 102(e) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as being unpatentable over Lam et al. US Patent No. 5,640,489 (102(e) date of at least 6/19/91) (Lam et al.). Applicants respectfully traverse this rejection.

Applicants respectfully submit that each and every element of claims 1-8, 10-15 and 37-39 is not taught or suggested by Lam et al. Lam et al. (as acknowledged by the Examiner at page 6 lines 1-2 of the previous Office Action mailed on July 28, 2000) teaches synthesis of a random library of biopolymers on beads, wherein each bead contains a single biopolymer. See Column 4, lines 18-23 of Lam et al. Lam et al. does not teach or suggest a preselected array of diverse biological polymers, whereby the diverse biological polymers occupy different regions of the substrate. Lam et al is directed to a single bead acting as a single substrate having only a single biopolymer. The Examiner suggests that the claimed solid support can include an embodiment of beads arranged in a spatially defined pattern such as being partitioned in microtiter plate wells, which the Examiner states is taught by Lam et al. However, even assuming that Lam et al teaches such an embodiment, any such embodiment would still be a random distribution and not a preselected array as claimed by applicants.

Additionally, there is no teaching or suggestion in Lam et al. to measure the presence of diverse unbound biological polymers as an indicator of the efficiency of the synthesizing step.

Instead, Lam et al. teaches bulk measurement of all components, especially free amino acids, present in a sample. Such teaching is evident in column 34, lines 25-36 of Lam et al., which states "a sample from each tube was tested with ninhydrin reagent." Therefore, Lam et al. does not teach measurement of the presence of diverse unbound biological polymers, but instead teaches measurement of the presence of free amino acids, as ninhydrin is commonly used by those skilled in the art as an indicator of the presence of free amino acids (see Exhibit A attached hereto).

Furthermore, the examples of Lam et al. fail to teach or suggest the synthesis of a preselected array of diverse biological polymers on a solid substrate as claimed by applicants. On page 5, paragraph 11 of the Office Action, the Examiner references applicants to see Column 39, example 10.1.1, Column 43, example 11, and Column 46, example 12. Applicants submit that these examples teach or suggest using a random library, wherein each bead contains a single biopolymer, and the examples do not teach or suggest synthesizing a preselected array of diverse biological polymers on a solid substrate as claimed by applicants. Example 10.1.1 in Column 39 specifically teaches that "Randomization was carried out in the next five coupling steps." See Column 39, lines 33-34. Therefore, applicants submit that example 10.1.1 specifically teaches synthesis of a random library. With reference to example 11 in Column 43, this example teaches that a "Restricted random library was used." See Column 43, lines 44-46. Additionally, example 11 teaches "random coupling steps." See Column 43, lines 57-59. Therefore, applicants submit that example 11 specifically teaches synthesis of a random library. With reference to example 12 in column 46, this example teaches synthesis of a peptide. In view of the specification, one skilled in the art would recognize that example 12 teaches synthesis of a

peptide on a resin, wherein each bead of the resin contains a single biopolymer. See column 4, lines 18-23 and Column 46, lines 13-14. Therefore, applicants submit that example 12 does not teach or suggest synthesis of a preselected array of diverse biological polymers on a solid substrate, wherein the diverse biological polymers occupy different regions of the solid substrate. Because, Lam et al. fails to teach or suggest each and every element of applicants' claimed subject matter, applicants respectfully request that the Examiner withdraw his rejection based on 35 U.S.C. § 102(e).

The Examiner is further respectfully requested to withdraw his rejection of the claimed subject matter as being obvious in view of Lam et al. for the reasons stated above. To establish prima facie obviousness, all the claim limitations must be taught or suggested by the prior art. See *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). As discussed above, Lam et al. does not teach or suggest synthesizing a preselected array of diverse biological polymers, whereby the diverse biological polymers occupy different regions of the substrate, and measuring the presence of diverse unbound biological polymers as an indicator of the efficiency of the synthesizing step. No reference has been identified to address these claim limitations and the Examiner has provided no rationale why one skilled in the art would be motivated to modify the teachings of Lam et al. to arrive at applicants' claimed invention other than stating that Lam et al teaches the analysis of arrays of molecules and that planar arrays are known. Even with this teaching, Lam et al. does not disclose analysis of arrays of molecules ***in the manner claimed by applicants*** , i.e. synthesizing a preselected array of diverse biological polymers occupying different regions of the substrate, cleaving diverse biological polymers from the solid substrate

thereby creating a mixture of diverse unbound biological polymers, and measuring presence of diverse unbound biological polymers as an indicator of the efficiency of the synthesizing step.

Accordingly, applicants respectfully request that the Examiner withdraw the rejection of claims 1-8, 10-15 and 37-39 under 35 U.S.C. § 102(e) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over Lam et al.

IV. Claims 1-8, 10-15 and 37-39 Are Patentable Over Lam et al. In View of Holmes

At page 3, paragraph 9, claims 1-8, 10-15 and 37-39 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lam et al. US Patent No. 5,640,489 in view of Holmes US Patent No. 5,679,773 and applicants' disclosure of the prior art teachings. The Examiner emphasizes that the embodiment of Holmes discussed at Column 19 lines 33-58 discusses the cleavage of array members from a support and comparison with standards to provide a confirmation of synthesis fidelity. Applicants respectfully traverse the rejection.

As discussed above, Lam et al. teaches against the use of a preselected array of diverse biological polymers on a solid substrate and does not teach or suggest measuring the presence of diverse unbound biological polymers as an indicator of the efficiency of the synthesizing step. Furthermore the Examiner's reference of Column 10, lines 57-59 in Lam et al. (see page 7, paragraph 12 of the Office Action mailed on March 22, 2001) discloses a method to synthesize peptides. In view of the specification, applicants submit that the method referred to in Column 10, lines 57-59 of Lam et al. requires addition of **a set of amino acids** to aliquots of reagents, e.g. a solid phase support, to produce a peptide, wherein each bead of the solid phase support contains a single biopolymer. Applicants submit that addition of **a set of amino acids** will

produce a random library. Therefore, Lam et al does not teach a preselected array of diverse biological polymers.

Holmes fails to cure the deficiencies in Lam et al. Specifically, Holmes fails to teach or suggest at least synthesizing a preselected array of diverse biological polymers, whereby the diverse biological polymers occupy different regions of the substrate. No other reference is cited by the Examiner to cure these deficiencies. Accordingly, applicants respectfully request withdrawal of the rejection of claims 1-8, 10-15 and 37-39 under 35 U.S.C. § 103(a) over Lam et al. in view of Holmes and allowance of the claimed subject matter.

VI. Conclusion

Having addressed all outstanding issues, applicants respectfully request entry and consideration of the foregoing amendments and reconsideration and allowance of the case, or in the alternative, entry of the foregoing amendments to place the case in better condition for appeal. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is requested to telephone the undersigned at the number below.

Respectfully submitted,

Dated: July 19, 2001

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Version of Amendments With Markings To Show Changes Made

1. (Twice Amended) A method of monitoring polymer array synthesis on a solid substrate comprising:

(i) synthesizing a preselected array of diverse biological polymers connected to cleavable linkers on a solid substrate, whereby the diverse biological polymers occupy different regions of the substrate, and wherein the diverse biological polymers comprise nucleotides, nucleosides, phosphoramidites, carbohydrates or natural or synthetic amino acids;

(ii) cleaving diverse biological polymers from the solid substrate by cleaving the cleavable linkers, thereby creating a mixture of diverse unbound biological polymers; and

(iii) measuring presence of diverse unbound biological polymers as an indicator of the efficiency of the synthesizing step.

10. (Twice Amended) A method for measuring the effect of altering a polymer array synthesis protocol, comprising:

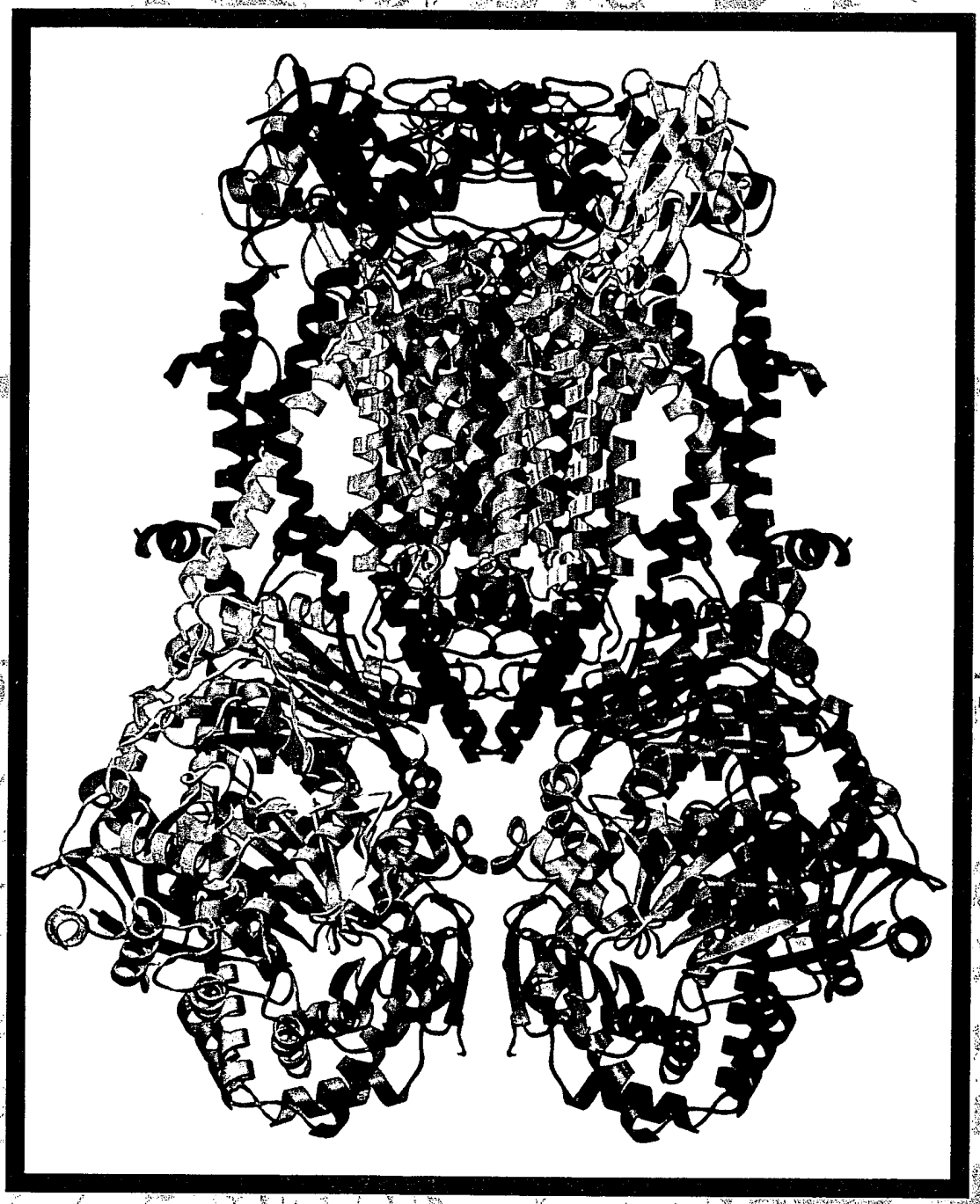
(i) synthesizing a preselected array of diverse biological polymers occupying different regions on a solid support by a first synthesis protocol, thereby creating a reference array of biological polymers, wherein the diverse biological polymers comprise nucleotides, nucleosides, phosphoramidites, carbohydrates or natural or synthetic amino acids;

(ii) synthesizing a preselected array of diverse biological polymers occupying different regions on a solid support synthesized by a second synthesis protocol, wherein the

second synthesis protocol is different than the first synthesis protocol, thereby creating a test array of biological polymers;

(iii) cleaving separately the reference array of biological polymers and the test array of biological polymers, thereby creating a mixture of diverse cleaved biological polymers from the reference array and a mixture of diverse cleaved biological polymers from the test array;

(iv) measuring presence of diverse cleaved biological polymers from the test array as an indicator of the efficiency of the first synthesis procedure and measuring presence of diverse cleaved biological polymers from the reference array as an indicator of the efficiency of the second synthesis procedure, thereby determining whether a difference between the first and second synthesis procedure affects the efficiency of the second synthesis procedure.



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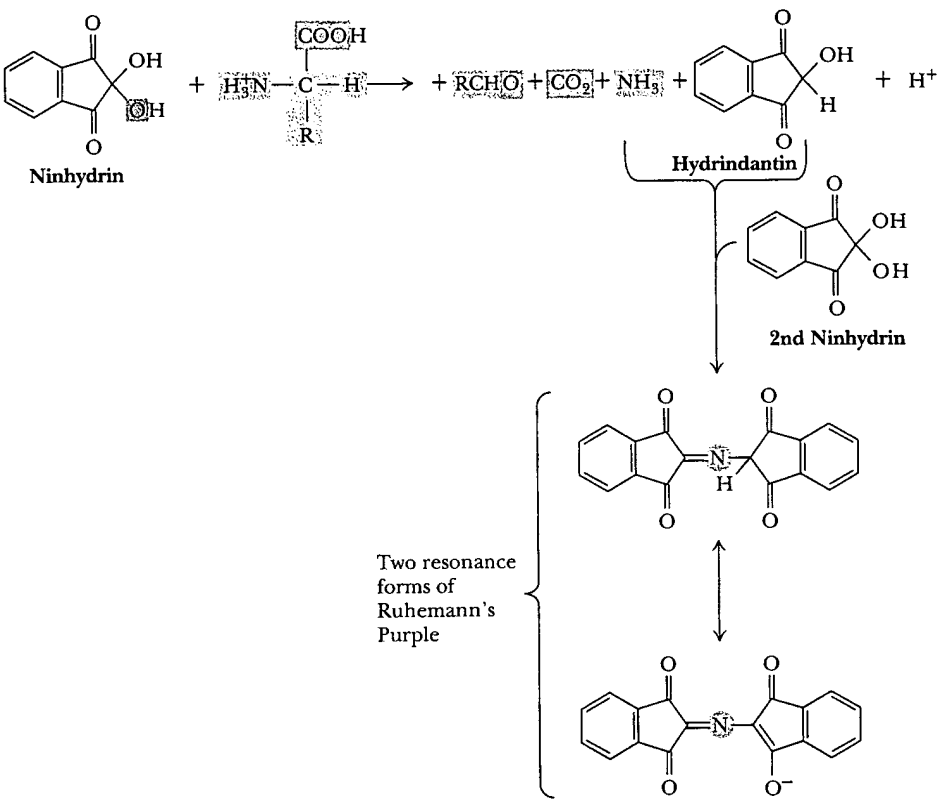
BIOCHEMISTRY

SECOND EDITION



IGURE 4.10 • The pathway of the ninhydrin reaction, which produces a colored product called "Ruhemann's Purple" that absorbs ght at 570 nm. Note that the reaction involves nd consumes two molecules of ninhydrin.

and acid chlorides are also readily formed. Esterification proceeds in the presence of the appropriate alcohol and a strong acid (Figure 4.9c). Polymerization can occur by repetition of the reaction shown in Figure 4.9d. Free amino groups may react with aldehydes to form Schiff bases (Figure 4.9e) and can be acylated with acid anhydrides and acid halides (Figure 4.9f).

The Ninhydrin Reaction

Amino acids can be readily detected and quantified by reaction with ninhydrin. As shown in Figure 4.10, *ninhydrin,* or triketohydrindene hydrate, is a strong oxidizing agent and causes the oxidative deamination of the α-amino function. The products of the reaction are the resulting aldehyde, ammonia, carbon dioxide, and hydrindantin, a reduced derivative of ninhydrin. The ammonia produced in this way can react with the hydrindantin and another molecule of ninhydrin to yield a purple product (Ruhemann's Purple) that can be quantified spectrophotometrically at 570 nm. The appearance of CO_2 can also be monitored. Indeed, CO_2 evolution is diagnostic of the presence of an α-amino acid. α-Imino acids, such as proline and hydroxyproline, give bright yellow ninhydrin products with absorption maxima at 440 nm, allowing these to be distinguished from the α-amino acids. Because amino acids are one of the components of human skin secretions, the ninhydrin reaction was once used extensively by law enforcement and forensic personnel for fingerprint detection. (Fingerprints as old as 15 years can be successfully identified using the ninhydrin reaction.) More sensitive fluorescent reagents are now used routinely for this purpose.

Specific Reactions of Amino Acid Side Chains

A number of reactions of amino acids have become important in recent years because they are essential to the degradation, sequencing, and chemical synthesis of peptides and proteins. These reactions are discussed in Chapter 5.